Remarks/Arguments

Claims 1, 6, 7, 10, 26, 27, 49 and 50 are currently amended. Claims 1-8, 10, 13-29 and 49-52 are pending in the application. Reconsideration is respectfully requested.

Request to Vacate the Office action

This latest Office action enters no less than ***thirteen*** new grounds of rejection over ***twenty six*** pages following a decision by the Board of Appeals. Not one of these rejections was suggested by the Board. The art rejections present numerous new combinations of ***twelve*** references. Several of the newly relied upon references have either been of record since the first action on the merits or have been considered in the initial office action in the form of an equivalent. Compare Edwards '837 and '309 and Platz '827, '968, and WO 96/32149, for example. None of the primary references relied upon in this action are truly "new." As discussed below, the Edwards references relied upon in three art rejections are duplicative, and Platz and Maa (which was a principal reference of the reversed rejection relied upon for the teachings relating to the inhaled powders) are no more relevant than any Edwards reference. The number of rejections, as well as the grounds of each rejection, made in this case are simply unnecessary and merely results in an unnecessary expenditure of Office and Applicant resources and denies Applicants of their patent term.

With respect to the various rejections relied on with differing secondary references, the secondary reference (Jensen) in several of these rejections were cited and considered in a similar obviousness rejection in the appeal, which was ***reversed***. The Examiner also added several new grounds of rejection based on a new secondary teaching, Christensen. While Christensen is related to aqueous injectable insulin formulations while Jensen relied on crystalline inhalable insulin formulations and, therefore, a distinction between the two can be articulated, Christensen is no more relevant (and arguably less relevant) to modifying light porous, inhalable spray-dried powders than Jensen. Thus, the reference is at best duplicative and each of these rejections is simply untimely.

Not one of these art rejections sets forth, or even attempts to set forth, a combination of references which presents a new substantive issue not already considered

by the Board in the earlier Decision. That is, the issue of each and every art rejection is the same as that previously considered, just relying on new references with substantially similar disclosures.

The language rejected as being indefinite has been present since the claims were originally filed. This Office action makes clear that Examiner Haghighatian decided to re-search the invention and completely re-exam the application, which is expressly forbidden under MPEP 1214.04. Further, the MPEP requires that:

> If the examiner has specific knowledge of the existence of a particular reference or references which indicate nonpatentability of any of the appealed claims as to which the examiner was reversed, he or she should submit the matter to the Technology Center (TC) Director for authorization to reopen prosecution under 37 CFR 1.198 for the purpose of entering the new rejection. See MPEP § 1002.02(c) and MPEP § 1214.07. ***The TC Director's approval is placed on the action reopening prosecution.***

(emphasis added). There is ***no*** evidence on this record that Examiner Haghighatian has submitted this Office action to the TC Director for approval. This application has been pending for over ***eight years***. Further, such an application is to receive personal SPE attention as well, also evidently missing from this action. MPEP 707.02. This office action does not suggest that the Examiner is committed to a fair examination or compact prosecution. This action gives the undersigned the impression that she is attempting to unnecessarily increase cost to the Applicants or their attorneys and to waste away patent term.

Vacation of the action and submission of the application to the TC Director before any additional prosecution, other than a Notice of Allowance, are respectfully requested.

Prosecution History Reference

There have been five Office Actions in the present case, including two Final Office Actions. The non-final Office Actions are referred to herein as "OA" followed by the mailing date of the OA; the Final Office Actions are referred to herein as "FOA" followed by the mailing date of the FOA. There has been one Examiner Answer to a Substitute Appeal Brief referred to herein as "EA" followed by the mailing date of the

EA, and one Decision on Appeal referred to herein as "Decision on Appeal dated February 24, 2009". Appellants have filed four responses, and one Substitute Appeal Brief. Appellants' responses are referred to herein as "AR" followed by the filing date of the response. Appellants' appeal is referred to herein as "AA" followed by the filing date of the appeal.

Claim Rejections 35 U.S.C. §112, second paragraph

Claims 1-8, 10, 13-29, and 49-52 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. OA mailed April 24, 2009. The Examiner states that claims 1, 6-8, 10, 26-27, and 49-50 contain the indefinite terms of "less than about" and/or "more than about", and that the said terms are indefinite because one of ordinary skill in the art cannot determine the scope of claimed ranges. The Examiner states that it is considered that "less than" or "more than" are set and determined limits, whereas "about" is an approximate term. The Examiner concludes that it is then not clear how a set range and an approximate term can be used together. The remaining claims are rejected for depending on a rejected base claim. OA mailed April 24, 2009, page 2, second paragraph. The Applicants respectfully disagree with the Examiner's conclusion.

Applicants submit that §112 does ***not*** require that every term be defined so explicitly. It is exceedingly rare for a patent specification to define the term "about" with a bright line test – such a definition would destroy its very purpose. Certainly, there is no *per se* rule that prohibits a patent applicant from combining the word about with a range (e.g., less than, greater than, exceeding or between). Indeed, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" was definite and could be clearly ascertained with a stopwatch.

The issue is whether the skilled practitioner would be able to understand the meaning of such terms in the context of the specification. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). As the level of skill in this art is high, wherein the ordinary skilled person has an advanced medical

and/or scientific degree (e.g. M.D., Ph.D., Pharm.D. or combinations thereof), a practitioner with one or more advanced degrees would not have difficulty ascertaining the meaning of the terms "less than about" or "or at least about" in the context of the present claims, particularly if a similar term can be ascertained with a stopwatch. *W.L. Gore.*

It is recognized that the term "at least about" in a claim was determined to be indefinite when there was close prior art and there was nothing in the specification, prosecution history or the prior art to provide any indication as to what range of specific activity is covered by the term "about". *Amgen, Inc. v. Chugai Pharmaceutical Co.,* 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). However, the facts in the present application are very different. There is no "close prior art" that discloses, "a multivalent cation-containing component where in, the dry powder is spray-dried and has a total amount of multivalent metal cation which is more than about 10% w/w of the total weight of the agent, a tap density of less than about 0.4g/cm^3, a median geometric diameter of between about 5 micrometers and about 30 micrometers and an aerodynamic diameter of from about 1 to about 5 microns" (amended Claim 1). In addition, in describing the amount of multivalent metal cation in the dry powder, the specification uses the explicit wording "about" and provides examples of ranges "… such as, about 2%, about 3%, about 4%, about 5%, etc.", or even, "… from about 1.5% w/w to about 2% w/w, or from about 2% w/w to about 2.5% w/w, or from about 2.5% w/w to about 3% w/w, etc…." Specification at page 9, lines 4-9. Similarly, the specification discloses, "… particles can have a tap density of less than about 0.4g/cm^3", and, "More preferred are particles having a tap density less than about 0.1 g/cm^3." Specification at page 17, lines 22-25. Claim 1 recites, "… a tap density of less than about 0.4g/cm^3…." Therefore, in regard to the amount of multivalent cation and tap density taught in claim 1, the skilled practitioner is provided with guidance as to what range the term covers in the teachings of the specification. Thus, Claims 1-8, 10, 13-29, and 49-52 are clear and not indefinite.

To further establish that there is no *per se* rule against the combination of the word "about" with a numerical range, the phrase "at least about" alone has been accepted in the claims of over 71,000 granted patents since 1975. This clearly establishes that the phrase is common. In such a situation, more is required from the PTO to establish that

the claim is indefinite than merely questioning how a set range and an approximate term can be used together.

Nonetheless, the claims have been amended to read in a manner similar to that which this Examiner proposed in another application in an effort to advance prosecution. Applicants submit that the scope of the claims is clear in either form and respectfully request reversal of the rejection.

Claim Rejections-35 U.S.C. §103

Edwards '064 in view of Jensen

Claims 1-8, 10, 13-29, and 49-52 are rejected under 35 U.S.C. §103(a) as being unpatentable over Edwards et al. (5,874,064) in view of Jensen et al. (6,043,214). OA mailed April 24, 2009. The Examiner states that Edwards et al. (5,874,064) teach aerodynamically light particles for drug delivery to the pulmonary system including tap density, diameter and aerodynamic diameter. The Examiner acknowledges that Edwards lacks disclosure on a multivalent metal cation, and states that Jensen (6,043,214) et al. cures this deficiency since, in a preferred embodiment, Jensen et al. teach preparation of a therapeutic powder formulation comprising particles composed of insulin or an analogue thereof, an enhancer, and zinc (see Col. 3, lines 41-47). The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made given the teachings of Edwards et al. to have looked in the art for other varieties of active agents for ultimate benefit from the treatment such as insulin zinc as taught by Jensen et al. with reasonable expectation of successful administration of light particles to the patients pulmonary system. Applicants respectfully disagree.

This rejection is not unlike that made in the appeal and reversed. In that rejection, the Examiner relied upon Maa as teaching everything but metal cation. She relied upon Jensen to state that it would be obvious to add a metal cation. That rejection was reversed. The Examiner makes no effort to explain why Edwards is more material than Maa. Certainly, Edwards was of record at the time the first action was made. Had this reference been better than (as compared to equivalent to) Maa, the Examiner was obligated to cite it at that time. She did not. *This rejection should be withdrawn because*

it is procedurally untimely and clearly no more relevant than rejections already decided upon.

As explained in the Brief on Appeal and considered by the Board, Applicant's specification teaches "the unexpected discovery that complexation of a multivalent metal cation with a therapeutic, prophylactic or diagnostic agent in carrying a negative, and therefore opposite charge to that of the cation, results in a *sustained release profile* of the agent upon pulmonary delivery." Specification page 2, lines 19-22. Jensen (6,043,214) states that the invention disclosed therein is directed towards a method of producing a therapeutic powder formulation by a process involving precipitation of an aqueous solution comprising insulin, an enhancer, and *optionally zinc* (see, Col. 2, lines 41-54). Jensen further states that the powder formulation produced by the process disclosed therein has enhanced features, such as *stability and flowability*, as compared to the same formulation produced by spray drying, freeze spray drying, vacuum drying and open drying (see Col 2, lines 55-67), and that the process of the invention disclosed therein is preferably carried out so as to obtain a substantially crystalline product (see, Col. 4, lines 4-8). Jensen never discloses or suggests the complexation of a multivalent metal cation (e.g. zinc) with a therapeutic, prophylactic or diagnostic agent carrying a negative, and therefore opposite, charge to that of the cation for the purpose of sustained release of an agent.

In addition, Jensen's disclosure of a process for preparing a formulation by precipitation teaches away from the presently claimed invention, as well as from the Examiner's instant example of particle formation using spray drying by Edwards (5,874,064) (see Example 3). Jensen specifically states that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. In other words, *Jensen himself teaches that the products possess the properties described therein because of the process used to produce the products*. Applicants have previously amended the claims to recite additional features that the powder compositions of the instant invention comprise, such as tap densities of less than 0.4 g/cm^3, aerodynamic diameters of from about 1 to about 5 microns and particle sizes of about 5 to about 30 microns. AR filed May 20, 2004. The ability to control the range of the tap density, aerodynamic diameter

and particle size of powders of the invention relies on the spray-drying process by which the powder compositions of the present invention are produced.

In contrast, Jensen's disclosed precipitation process does not provide a means for controlling or achieving the tap density, aerodynamic size or average particle size of the powder formulations resulting from the precipitation process. The precipitation process disclosed by Jensen yields crystals. These crystals are the result of allowing a spontaneous amorphous precipitate to rest for a period of time to allow the formation of crystals which are then dried to form the dry powder disclosed therein. The crystals resulting from the precipitation process described by Jensen are whatever size and shape that the precipitation process yields. Jensen does no more than measure the size of the resulting crystals. Therefore, one skilled in the art would not look to a precipitation process such as that disclosed by Jensen if the skilled practitioner was concerned about controlling the tap density, aerodynamic diameter and particle size of the final powder product as is presently claimed.

Further, the *optional* addition by Jensen of zinc during particle formation to enhance features of the crystal such as stability and flowability, by a process that teaches away from that of the specification, is in no way relevant to the addition of a multivalent metal cation for the purpose of obtaining a sustained release profile as taught in the specification, much less at the claimed cation concentration. As Jensen discloses a fundamentally different process of particle formation that teaches away from the formulations produced by spray drying disclosed in Edwards, there is no motivation to combine Jensen with Edwards as the Examiner has done (*Tec Air, Inc. v. Denso Manufacturing Michigan Inc.,* 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) ("There is no suggestion to combine ... if a reference teaches away from its combination with another source")). Even if one were motivated by Edwards to prepare particles having the listed properties, Edwards does not teach how one would accomplish this goal using the process of Jensen.

In the Decision on Appeal dated February 24, 2009, the Appeal Board concluded that the combination of references having differences in their objectives, such as the physical properties required by the present claims and the means to achieve those properties, failed to support an obviousness rejection of the present claims. (Decision on

Appeal dated February 24, 2009, page 12) The Examiner has done no more than substitute one reference for another.

Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. Applicants respectfully request reversal of the rejection.

Edwards '309 in view of Christensen

Claims 1-8, 10, 13-17, 21, 24-28, and 49-51 are rejected under 35 U.S.C. §103(a) as being unpatentable over Edwards et al. (5,985,309) in view of Christensen (3,102,077). OA mailed April 24, 2009. The Examiner states that Edwards et al. teach particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system. The Examiner continues by stating that the deficiency of Edwards '309 is the lack of specifically disclosing the multivalent cation component, which is said to be cured by Christensen, who teaches preparations of zinc containing 2.75 to 8% zinc. The Examiner concludes by stating that while Edwards et al. do not anticipate the claimed formulations, they teach advantages of combining proteins such as insulin with charged molecules. As Christensen discloses the combination of a zinc salt with insulin and the advantages of doing so, the Examiner reasons that it would have been obvious to do so. Applicants respectfully disagree.

Christensen does not disclose dry powder formulations of insulin and zinc. Instead Christensen discloses aqueous zinc-containing insulin suspensions for use in the treatment of diabetic patients wherein the insulin is in crystalline or amorphous form (Col. 6, lines 73-75). To achieve the zinc/insulin compounds disclosed in Christensen, it is necessary to follow a specific 3 stage process (see Col. 5, line 61 through Col. 6, line 34). The zinc/insulin crystals formed by this process have specific characteristics as determined by X-ray powder crystallography (Col. 5, lines 5-60). Christensen provides a detailed explanation of the precise manner in which zinc and chloride ions become complexed with the insulin molecule as a result of the specific process steps outlined by Christensen (see Col. 5, lines 40-61).

The spray-drying methods of Edwards do not include the critical steps outlined by Christensen. Thus the particles disclosed in Edwards are fundamentally different than

those disclosed by Christensen and any modification of Christensen such as to produce zinc containing particles in accordance with the methods of Edwards would destroy the fundamental characteristics of the Christensen particles and the same would be true of the characteristics of the Edwards '309 particles if one were to modify the particle production process of Edwards to use the 3 stage process of Christensen. As discussed in MPEP 2143.01 "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)".

Again, in the Decision on Appeal dated February 24, 2009, the Appeal Board concluded that the combination references having differences in their objectives such as the physical properties required by the present claims and the means to achieve those properties, failed to support an obviousness rejection of the present claims. (Decision on Appeal dated February 24, 2009, page 12) The Examiner has done no more than substitute combinations of other references that are no more relevant than the combination reviewed by the Appeal Board.

In addition, neither reference discloses or suggests that the total amount of multivalent metal cation is more than about 10% w/w of the total weight of the agent as is presently claimed. The highest amount of zinc content taught by Christensen is 8%. Therefore, neither reference provides all of the claimed elements as is asserted by the Examiner.

The Examiner has failed to establish that the claims are *prima facie* obvious in view of the cited combination of references. Reversal of the rejection is respectfully requested.

Edwards '295 in view of Jensen

Claims 1-8, 10, 13-19, 21-29, and 49-52 are rejected under 35 U.S.C. §103(a) as being unpatentable over Edwards et al. (6,136,295) in view of Jensen et al. (6,043,214). OA mailed April 24, 2009. Edwards '295 is a divisional application of Edwards '064. It appears that this rejection should be identical to the first rejection made above. The duplication of the rejections is completely unnecessary and unduly increases the costs of

prosecution. This is particularly true since the Examiner's discussion of Jensen differs, suggesting that the rejection is actually different. The arguments made above are equally relevant to this rejection but will be repeated here out of fear that Examiner Haghighatian will hold a reply which does not repeat the argument as non-responsive.

The Examiner states that Edwards et al. (6,136,295), referred to herein as "Edwards '295", teach aerodynamically light particles for drug delivery to the pulmonary system, and that methods for their synthesis and administration are provided. The Examiner acknowledges that Edwards '295 lacks disclosure of a multivalent metal cation such as zinc, and states that Jensen (6,043,214) et al. cures this deficiency by disclosing the preparation of a therapeutic powder formulation comprising particles composed of insulin or an analogue thereof, an enhancer, and zinc (see Col. 3, lines 41-47). The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the invention was made, given the teachings of Edwards '295, to have looked in the art for other varieties of active agents for ultimate benefit from the treatment such as insulin zinc as taught by Jensen et al. Applicants respectfully disagree.

As explained above, Jensen (6,043,214) states that the invention disclosed therein is directed towards a method of producing a therapeutic powder formulation by a process involving precipitation of an aqueous solution comprising insulin, an enhancer, and *optionally* zinc (see, Col. 2, lines 41-54). Jensen further states that the powder formulation produced by the process disclosed therein has enhanced features, such as stability and flowability, as compared to the same formulation produced by spray drying, freeze spray drying, vacuum drying and open drying (see Col 2, lines 55-67), and that the process of the invention disclosed therein is preferably carried out so as to obtain a substantially crystalline product (see, Col. 4, lines 4-8).

In this rejection, the Examiner discusses the disclosure in Jensen (see Col. 3, lines 41-47) stating that zinc is preferably present in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer is not evidence that zinc should be added to the Edwards formulations or be present in an amount that is more than 10% w/w of the total weight of the agent. The molecular weight of insulin is 5808. Thus the molecular weight of an insulin hexamer is around 53,000. The molecular weight of zinc is around 65. Thus the molecular weight of 12 zinc atoms is about 780. Thus, even if 12

zinc atoms are present for every insulin hexamer, this is far less than 10% w/w of the total weight of the insulin (more like 0.02%). Edwards also lacks disclosure or suggestion of the content of zinc in accordance with the present claims. Therefore, the cited combination of references also fails to provide a disclosure of all the claimed elements as is asserted by the Examiner.

As explained above, Jensen's disclosure of a process for preparing a formulation by precipitation teaches away from the presently claimed invention which requires that the particles be "spray dried". While Edwards '295 discloses spray-dried particles, Jensen specifically states that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. The crystals resulting from the precipitation process described by Jensen are highly variable and are whatever size and shape that the precipitation process yields. Jensen does no more than measure the size of the resulting crystals.

As Jensen discloses a fundamentally different process of particle formation that that results in fundamentally different particle morphologies such as those produced by spray drying disclosed in Edwards '295, there is no motivation to combine Jensen with Edwards '295 as the Examiner has done (*Tec Air, Inc. v. Denso Manufacturing Michigan Inc.,* 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) ("There is no suggestion to combine ... if a reference teaches away from its combination with another source")). Even if one were motivated by Edwards '295 to prepare particles having presently claimed properties, neither reference discloses the means to accomplish this with any expectation of success given the specific and divergent goals of each reference relating to particle morphology.

In the Decision on Appeal dated February 24, 2009 (pages 11-12), the Appeal Board concluded that the combination with Jensen and other references having different objectives such as the physical properties required by the present claims failed to support an obviousness rejection of the present claims. The Examiner has done no more than substitute another reference in combination with Jensen that is no more relevant than the combination reviewed by the Appeal Board.

Therefore, the Examiner has failed to establish that the claims are *prima facie* obvious in view of the cited combination of references. Reversal of the rejection is respectfully requested.

Vanbever '678 in view of Christensen

Claims 1-8, 10, 13-29, and 49-52 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vanbever et al. (7,052,678) as evidenced by Christensen (3,102,077). OA mailed April 24, 2009. It is noted that Vanbever '678 was filed after the filing date of this application and is a CIP of the Edwards patents and corresponding applications discussed above. Thus, it is clear that the portion of Vanbever that constitutes prior art is no more relevant than the three Edwards documents discussed above. The Examiner makes ***no effort*** to identify the portions of Vanbever which qualify as prior art and that portion that is not. It is not the Applicants' responsibility to do this task for the Examiner and the undersigned will not at this very late stage of prosecution. It is interesting to note the Examiner's liberal use of the cut-and-paste function in making this rejection where she inappropriately referred to an unidentified Edwards disclosure to conclude the rejection. Is that because she recognizes the substantial identity in the relevant part of the disclosures? These fundamental errors in articulating the rejection make it impossible to meaningfully respond. The duplication of the rejections is completely unnecessary and unduly increases the costs of prosecution.

The Examiner states that Vanbever et al. teach a method for pulmonary delivery of therapeutic, prophylactic and diagnostic agents to a patient wherein the agent is released in a sustained fashion, and to particles suitable for use in the method, with an effective amount of particles comprising a polycationic complexing agent (as compared to a metal cation) which is complexed with a therapeutic, prophylactic or diagnostic agent. The Examiner continues by stating that Vanbever et al. teach that most preferably, the polycationic agent, protamine, is complexed with insulin (Col. 5, lines 45-47), and that the particles can further comprise a multivalent metal cation such as zinc, calcium, etc. (see Col. 6, lines 58-67). The Examiner acknowledges that Vanbever, however, does not clearly disclose the amount of zinc to be added to the powder formulation of insulin. Christensen, who teaches preparations of zinc containing 2.75 to 8% zinc, is said

to cure this deficiency. Christensen is said to disclose production of zinc-insulin in amorphous or crystalline form with a chemically bound zinc content of as high as 6% and even up to about 8% (see Col. 2, lines 26-31). The Examiner concludes that while Edwards et al. [*sic*] does not teach the claimed powder formulations (*note that Applicants understand the Examiner to mean Vanbever et al. (7,052,678), not Edwards et al.*), because Christensen discloses the combination of zinc salt with insulin and the advantages of doing so, it would have been obvious to one of ordinary skill in the art to, essentially, add more zinc. Applicants respectfully disagree.

As discussed above, Christensen does not disclose dry powder formulations of insulin and zinc. Instead Christensen discloses aqueous zinc-containing insulin suspensions for use in the treatment of diabetic patients wherein the insulin is in crystalline or amorphous form (Col. 6, lines 73-75). To achieve the zinc/insulin compounds disclosed in Christensen, it is necessary to follow a specific 3 stage process (see Col. 5, line 61 through Col. 6, line 34). The zinc/insulin crystals formed by this process have specific characteristics as determined by X-ray powder crystallography (Col. 5, lines 5-60). Christensen provides a detailed explanation of the precise manner in which zinc and chloride ions become complexed with the insulin molecule as a result of the specific process steps outlined by Christensen (see Col. 5, lines 40-61).

The present claims require that the particles are spray dried. The spray-drying methods of Vanbever do not include the critical steps outlined by Christensen and will not result in the novel zinc-containing insulin molecules disclosed in Christensen. Thus the particles disclosed in Vanbever are fundamentally different than those disclosed by Christensen and any modification of Christensen such as to produce zinc containing particles in accordance with the methods of Vanbever would destroy the fundamental characteristics of the Christensen particles. As discussed in MPEP 2143.01 "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)".

In the Decision on Appeal dated February 24, 2009, the Appeal Board concluded that the combination references having differences in their objectives such as the physical

properties of the particles required by the present claims and the means to achieve those properties, failed to support an obviousness rejection of the present claims. The Examiner has done no more than substitute combinations of other references that are no more relevant than the combination already reviewed by the Appeal Board.

The Examiner has failed to establish that the claims are *prima facie* obvious in view of the cited combination of references. Reversal of the rejection is respectfully requested.

Platz '827 in view of Jensen

Claims 1-8, 10, 13-17, 21, 24-28, and 49-51 are rejected under 35 U.S.C. §103(a) as being unpatentable over Platz et al. (7,097,827) in view of Jensen et al. (6,043,214). OA mailed April 24, 2009.

Platz is a patent issuing from an application filed on September 13, 2002, *after* the filing date of the present application. It claims priority to an application, the corresponding PCT of which was considered at the time of the first action on the merits. Had the Examiner felt that this reference was more relevant than the prior relied upon at that time, she should have made the rejection then. This rejection is clearly inappropriate at this late stage of prosecution. The Examiner further makes no effort to explain that portion of Platz which is prior art.

The Examiner states that Platz et al. teach dispersible dry powder pharmaceutical-based compositions with a particle size of about 1-5 μm mass median diameter (MMD), and preferably 1-3 μm MMD; a delivered dose of about >30%, and most preferred >60%; and an aerosol particle size distribution of about 1-5 μm mass median aerodynamic diameter (MMAD), usually 1.5-4.5 μm MMAD, and preferably 1.5-4 μm MMAD (see Abstract and Summary). Suitable active agents include polypeptides and proteins such as insulin (Col. 6, lines 3-10) and suitable excipients include polysaccharides and amino acids. The Examiner alleges, *wrongfully*, that Platz also discloses a 20% insulin formulation for pulmonary delivery that includes zinc citrate and is spray dried to form powders.

Firstly, Platz does not provide a ***prior art*** disclosure of a tap density of less than 0.4 g/cm^3 that has a priority date prior to the earliest priority date of the present

application or the median geometric diameter limitation in combination with the described aerodynamic diameter. As discussed in detail in the Appeal Brief filed on July 13, 2009, in copending application 11/523,914, the '827 patent issued from an application filed September 13, 2002, therefore, the filing date of the application is *after* the effective filing date of the present claims. Thus the '827 patent and its claims are not *per se* prior art for what is described and claimed in the application *as filed* on September 13, 2002. The '827 patent can only be relied upon for what is *actually disclosed* in the original priority document as filed in April 14, 1995. The *claims* that issued in the '827 Patent were simply *not described* in 1995. These were *added* in *2002*. Thus, these later filed claims *cannot* be relied on to support this rejection. One *must* turn back to the original 1995 specification and identify what *that* specification discloses and there is absolutely no discussion in the '827 specification anywhere regarding a range of tap densities or specific tap densities.

The fact that this rejection adds the additional technical issue of Platz's effective filing date for the physical parameters of the products described clearly establishes that this reference is less relevant than the Edwards disclosures. For this reason alone, this rejection should be withdrawn as being duplicative.

Secondly, Platz does not teach the use of zinc citrate, as alleged by the Examiner. It uses ***sodium*** citrate, which is ***not*** a multivalent metal cation-containing component. Example 1. *Given the very late stage of prosecution in this case, the Examiner should take more care in characterizing references.*

The deficiencies in the reference are said to be cured by Jensen et al., since in a preferred embodiment, Jensen et al. allegedly teach the preparation of a therapeutic powder formulation comprising particles composed of insulin or an analogue thereof, an enhancer, and zinc preferably in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer (see Col. 3, lines 41-47), for substantially the same reasons discussed above.

Nonetheless, as established above, Jensen does not cure the deficiencies of Platz et al. First, with regard to the Examiner's statement that Jensen discloses that the total amount of multivalent metal cation is more than about 10% w/w of the total weight of the agent as is presently claimed, this is incorrect. The Examiner's citation of the passage in

Jensen (see Col. 3, lines 41-47) stating that zinc is preferably present in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer is not evidence that zinc is present in an amount that is more than 10% w/w of the total weight of the agent. The molecular weight of insulin is 5808. Thus the molecular weight of an insulin hexamer is around 53,000. The molecular weight of zinc is around 65. Thus the molecular weight of 12 zinc atoms is about 780. Thus, even if 12 zinc atoms are present for every insulin hexamer, this is far less than 10% w/w of the total weight of the insulin (more like 0.02%).

In addition, Jensen's disclosure of a process for preparing a formulation by precipitation teaches away from the presently claimed invention which requires that the particles be "spray dried". While Platz discloses spray-dried particles, Jensen specifically states that that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. The crystals resulting from the precipitation process described by Jensen are highly variable and are whatever size and shape that the precipitation process yields. Jensen does no more than measure the size of the resulting crystals. One skilled in the art would not look to a precipitation process such as that disclosed by Jensen if the skilled practitioner was concerned about controlling the tap density, aerodynamic diameter and particle size of the final powder product as is presently claimed.

As Jensen discloses a fundamentally different process of particle formation that results in fundamentally different particle morphologies such as those produced by spray drying disclosed in Platz, there is no motivation to combine Platz with Jensen as the Examiner has done (*Tec Air, Inc. v. Denso Manufacturing Michigan Inc.,* 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) ("There is no suggestion to combine ... if a reference teaches away from its combination with another source")). Even if one were motivated by Platz to prepare particles having presently claimed properties, neither reference discloses the means to accomplish this with any expectation of success given the specific and divergent goals of each reference relating to particle morphology.

In the Decision on Appeal dated February 24, 2009 (pages 11 and 12), the Appeal Board concluded that the combination with Jensen and other references having different objectives such as the physical properties required by the present claims failed to support

an obviousness rejection of the present claims. The Decision on Appeal also stated (with reference to a combination of Jensen with another reference) that the Examiner failed to establish that any of the powders would have had the physical properties required by the claims given the many differences between the methods and their starting materials (page 12). Given that neither reference discloses the claimed amount of zinc or the claimed tap densities, the same is true for the combination of Platz and Jensen. The Examiner has done no more than substitute another reference in combination with Jensen that is no more relevant than the combination already reviewed by the Appeal Board.

Therefore, the Examiner has failed to establish that the claims are *prima facie* obvious in view of the cited combination of references. Reversal of the rejection is respectfully requested.

Maa in view of Christensen

Claims 1-8, 10, 13-17, 26-27, and 49-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Maa et al. (6,284,282) in view of Christensen (3,102,077). OA mailed April 24, 2009. Maa was a principal reference in the rejection reversed by the Appeal Board. Christensen clearly adds nothing over and above what Jensen added. This rejection is clearly untimely on its face and should be withdrawn.

The Examiner states that Maa et al. discloses a method of spray freeze drying proteins for pharmaceutical administration (Col. 2, lines 10-20) having the claimed particle sizes, tap density and aerodynamic diameters. The Examiner states that Maa et al. discloses proteins which include insulin (Col. 6, line 46) and other components. The Examiner concedes that Maa lacks specific disclosure on addition of a multivalent metal cation.

Maa is clearly less relevant than Edwards as Maa is limited to freeze dried products and the claims are directed to spray dried products. Thus, this rejection is duplicative with the above rejections over Edwards and should be withdrawn for that reason alone. Nonetheless, the deficiency in the omitted teaching of adding zinc is said to be cured by Christensen.

As above, the Examiner states that Christensen teaches preparation of insulin containing 2.75 to 8% zinc, and discloses that zinc-insulin amorphous or crystalline form

with chemically bound zinc content of as high as 6% and even as high as 8% (see Col. 2, lines 26-31). The Examiner also states that Christensen discloses that amorphous insulin may be used instead of crystalline insulin.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Maa et al. on spray dried powder formulations containing proteins and peptides such as insulin, with a tap density of less than 0.1 and particle size of from 5 to 30 microns with the teachings of Christensen on insulin powders with high content of zinc, with a reasonable expectation of successful delivery of a sustained release insulin formulation to the patient's pulmonary system for better control of disorders such as diabetes. Applicants respectfully disagree.

As discussed above, Christensen does not disclose dry powder formulations of insulin and zinc and also does not disclose or suggest that the total amount of multivalent metal cation is more than about 10% w/w of the total weight of the agent as is presently claimed. Instead Christensen discloses aqueous zinc-containing insulin suspensions for use in the treatment of diabetic patients wherein the insulin is in crystalline or amorphous form (Col. 6, lines 73-75) and wherein the zinc is present in the range of less than 10% w/w of the total weight of the insulin (7% zinc content is the highest amount of zinc exemplified). To achieve the zinc/insulin compounds disclosed in Christensen, it is necessary to follow a specific 3 stage process (see Col. 5, line 61 through Col. 6, line 34)). The zinc/insulin crystals formed by this process have specific characteristics as determined by X-ray powder crystallography (Col. 5, lines 5-60). Christensen provides a detailed explanation of the precise manner in which zinc and chloride ions become complexed with the insulin molecule as a result of the specific process steps outlined by Christensen (see Col. 5, lines 40-61). There is no disclosure or suggestion in Christensen that such complexation can occur using any method other than the method described therein.

The present claims require that the powdered particle composition be spray dried. Maa does not disclose spray drying but instead discloses a spray freeze drying process. Maa indicates that spray freeze drying results in specific physical properties that are superior to those of spray dried particles (Col. 1, lines 39-52). As discussed in the

Decision on Appeal dated February 24, 2009, the Appeal Board determined that even if the skilled person were motivated to use Maa's spray freeze drying process to prepare a powder from a differing starting material which in this instance is Christensen's starting composition, the Examiner has not provided any rational basis for concluding that spray dried powders would have been expected to have the physical properties required by the present claims given that Maa specifically indicates that the spray-freeze dried powders disclosed therein differ from spray-dried powders. The Examiner has done no more than substitute other references in combination with Maa that are no more relevant than the combination already reviewed by the Appeal Board.

Therefore, the Examiner has failed to establish that the claims are *prima facie* obvious in view of the cited combination of references. Reversal of the rejection is respectfully requested.

Claim Rejections- Nonstatutory obviousness-type double patenting.

Edwards 5,985,309 in view of Christensen

Claims 1-8, 10, 13-17, 21, 24-28, and 49-51 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,985,309 in view of Christensen (3,102,077). OA mailed April 24, 2009. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The Examiner states that the difference lies in that "the specific multivalent cation is not identified" in Edwards (indeed, the claims do not recite any multivalent metal cation), while in the instant application the multivalent cation is identified as zinc (the claims require a multivalent metal cation). The Examiner states that Christensen teaches that zinc insulin complexes are known and beneficial for sustained release therapy. The Examiner concludes that one of ordinary skill in the art would have been motivated to have looked in the art for specific multivalent metal cation suitable for combination with insulin, as taught by Christensen with reasonable expectation of success. Applicants respectfully disagree.

This rejection is substantially duplicative with the art rejection made under 35 USC §103 above. For all the reasons discussed above, this double patenting rejection is also in error.

Edwards '309 discloses particles for drug delivery to the pulmonary system consisting of a therapeutic agent and a material selected from the group consisting of surfactant and a molecule having a charge opposite to the charge of the therapeutic agent and forming a complex thereto … (claim 1, Col. 27, lines 33-37). A molecule having a charge opposite to the charge of the therapeutic agent is a generic term, and does not define the type of molecule to complex with the therapeutic agent, nor the nature of the opposite charge of the molecule complexing with the therapeutic agent. For example, a molecule having a charge opposite to the charge of the therapeutic would include a host of molecules from various families and types, having either a net negative or positive charge depending on the net charge of the therapeutic agent. Examples of molecules having a charge opposite to the charge of the therapeutic agent could be drawn from the families of peptides, carbohydrates, nucleic acids, polyamines, lipids, monovalent cations, and anions of various ionization states. Nowhere in the claims of Edwards is there specific language claiming use of a *multivalent metal cation*. The Examiner is misleading in her rejection argument when she states, "The difference is that in the U.S. Patent '309 the specific multivalent cation is not identified …". As per *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992), in a double patenting rejection, "it is important to bear in mind that comparison can be made only with what invention is *claimed* in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim *defines* and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference". *General Foods* at 1282. Also as noted in *General Foods*, "we are not here concerned with what one skilled in the art would be aware [of] from *reading* the claims, but what *inventions the claims define*". *General Foods at 1282* quoting *In re Sarett*, 327 F2d 1005, 1013.

The claims of Edwards do not *define* a specific charged molecule or the amount of the charged molecule. Given the myriad of choices for a "charged molecule" as is discussed above, the Examiner has provided no rational basis for the skilled person to

choose zinc as disclosed in Christensen or any other multivalent metal cation. Furthermore, the combination of Edwards with Christensen doesn't provide any suggestion or disclosure that the charged molecule be present in an amount of at least 10% w/w of the total amount of active agent as is presently claimed.

The present claims also require that the powder be spray dried. Neither the claims of Edwards nor Christensen disclose that the dried powder should be spray dried. As stated by the Appeal Board in the Decision on Appeal dated February 24, 2009, the requirement of spray drying in the present claims can not be ignored. Page 11, Decision on Appeal dated February 24 2009.

In view of the above discussion, the Examiner has failed to established obviousness-type double patenting between the referenced claims in combination with the cited art and the present claims. Withdrawal of the rejection is respectfully requested.

Vanbever in view of Jensen

Claims 1-8, 10, 13-17, 24-28, and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8-48 of U.S. Patent No. 7,052,678 ("Vanbever") in view of Jensen et al. (6,043,214). OA mailed April 24, 2009. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The Examiner alleges that the difference is said to lie in the use of a polycationic complexing agent while in the instant application the complexing agent is a multivalent metal cation. Jensen et al. is said to teach that zinc insulin complexes are known and beneficial for sustained release therapy. The Examiner concludes that one of ordinary skill in the art would have been motivated to substitute one complexing agent for another with reasonable expectation of success. Applicants respectfully disagree.

Again, this rejection is duplicative with the rejection made under 35 USC §103, discussed above. For all the reasons the obviousness rejection over the Vanbever disclosure taken as a whole must fall, the obviousness double patenting rejection over the Vanbever claims must fall.

The Examiner has provided no reasonable basis for asserting that the skilled person would modify the claims of Vanbever to replace the claimed polycationic complexing agent with a multivalent metal cation and particularly zinc as disclosed in Jensen. Claim 5 among others of Vanbever further defines the polycationic complexing agent as being protamine, spermine, spermidine, chitosan and polycationic polyamino acids. These agents are organic molecules having multiple charged units. None of these compounds contains a metal ion and there is no motivation for the skilled person to substitute a metal ion for the compounds recited in Vanbever's claims.

Furthermore, in contrast to what the Examiner states, i.e. "Jensen et al. teaches that zinc insulin complexes are known and beneficial for sustained release therapy", Jensen never discloses or suggests that the purpose for the complexation of a multivalent metal cation (e.g. zinc) with a therapeutic, prophylactic or diagnostic agent is for sustained release therapy, but rather states for the purpose of improving stability and flowability. See FF8 of the Decision on Appeal dated February 24, 2009.

The present claims also require that the powder be spray dried. Neither the claims of Vanbever nor Jensen disclose that the dried powder should be spray dried. As stated by the Appeal Board in the Decision on Appeal dated February 24, 2009, the requirement of spray drying in the present claims can not be ignored. Page 11, Decision on Appeal dated February 24 2009. The Examiner has also not established that the physical properties required by the present claims would be achieved upon replacing the polycationic molecules of Vanbever with the zinc molecule of Jensen. See page 12 of the Decision on Appeal dated February 24, 2009.

As discussed earlier, Jensen teaches away from the stabilized preparations disclosed in Vanbever. Jensen's dry powders are produced by a precipitation process that results in dry powders that are mostly crystalline particles. Jensen specifically states that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. In contrast, Vanbever claims particles for drug delivery to the pulmonary system consisting of specific tap densities; aerodynamic size and median geometric diameters (see claims 15-20, Col. 31, lines 54-66). The crystalline particles resulting from the precipitation process disclosed by Jensen are fundamentally different from those

disclosed in Vanbever. A precipitation process such as that disclosed in Jensen does not, by its nature, provide one skilled in the art with the means to control the formation of the crystals from the precipitate such that the resulting crystals are hollow and/or porous and possess desired tap density, aerodynamic and geometric sizes of the stabilized formulations of Vanbever. Therefore, one skilled in the art would not be motivated to combine Jensen and Vanbever, as Jensen teaches away from a process and a product such as that described in Vanbever.

In view of the above discussion, the Examiner has failed to establish obviousness-type double patenting between the referenced claims in combination with the cited art and the present claims. Withdrawal of the rejection is respectfully requested.

Edwards '837 in view of Jensen

Claims 1-8, 10, 13-17, 21, 24-28, and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. Edwards (US Patent 6,652,837) in view of Jensen et al. (US Patent 6,043,214). OA mailed April 24, 2009. The Examiner states that, although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The Examiner states that the difference is that in Edwards, the nature if the charged molecule is not identified, while in the instant application the active agent is complexed with a multivalent metal cation. Jensen et al. is stated by the Examiner to teach that zinc insulin complexes are known and beneficial for sustained release therapy. The Examiner concludes that one of ordinary skill in the art would have been motivated to look for specific charged molecules suitable for complexation with active agents such as insulin. Applicants respectfully disagree.

Again, this rejection must fall for all the reasons discussed above with respect to the other Edwards disclosures, particular Vanbever.

Furthermore, the Examiner is misleading when the Examiner states that, i.e. "Jensen et al. teaches that zinc insulin complexes are known and beneficial for sustained release therapy", Jensen never discloses or suggests that the purpose for the complexation of a multivalent metal cation (e.g. zinc) with a therapeutic, prophylactic or diagnostic

agent is for sustained release therapy, but rather states for the purpose of improving stability and flowability. See FF8 of the Decision on Appeal dated February 24, 2009.

The present claims also require that the multivalent metal cation be present in the amount of 10% w/w of the total weight of the agent. Neither Edwards nor Jensen disclose or suggest this feature of the present claims. The referenced claims of Edwards are silent with regard to this feature, and as discussed earlier, calculation of the amount of zinc disclosed by Jensen as compared to the total weight of the agent is less than 1 %.

The present claims also require that the powder be spray dried. Neither the claims of Edwards nor Jensen disclose that the powder is spray dried. As stated by the Appeal Board in the Decision on Appeal dated February 24, 2009, the requirement of spray drying in the present claims can not be ignored. Page 11, Decision on Appeal dated February 24, 2009.

As discussed earlier, Jensen teaches away from the stabilized preparations disclosed in Edwards. Jensen's dry powders are produced by a precipitation process that results in dry powders that are mostly crystalline particles. Jensen specifically states that that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. In contrast, Edwards claims particles for drug delivery to the pulmonary system consisting of specific tap densities, aerodynamic size and median geometric diameters (see claims 15-20, Col. 31, lines 54-66). The crystalline particles resulting from the precipitation process disclosed by Jensen are fundamentally different from those disclosed in Edwards. A precipitation process such as that disclosed in Jensen does not, by its nature, provide one skilled in the art with the means to control the formation of the crystals from the precipitate such that the resulting crystals are hollow and/or porous and possess desired tap density, aerodynamic and geometric sizes of the stabilized formulations of Edwards. Therefore, one skilled in the art would not be motivated to combine Jensen and U.S. Patent '837, as Jensen teaches away from a process and a product such as that described in Edwards.

In view of the above discussion, the Examiner has failed to establish obviousness-type double patenting between the referenced claims in combination with the cited art and the present claims. Withdrawal of the rejection is respectfully requested.

Lipp '835 in view of Jensen

Claims 1-8, 10, 13-17, 24-28, and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 of U.S. Patent No. 6,749,835 ("Lipp") in view of Jensen et al. (6,043,214). OA mailed April 24, 2009. The Examiner states that the claims of the U.S. Patent '835 are drawn to a method of delivery to the pulmonary system comprising administering to the respiratory tract of a patient an effective amount of a dry powder having the claimed tap density, geometric and aerodynamic diameters and comprising an active agent, a hydroxydicarboxylic acid, a phospholipid and a multivalent cation or anion. The Examiner alleges that the difference is that, in the U.S. Patent '835, depending claims are drawn to albuterol as the active agent and calcium as the multivalent metal cation. The Examiner also asserts that Jensen et al. teach that zinc insulin complexes are known and beneficial for sustained release therapy. The Examiner concludes that one of ordinary skill in the art would have been motivated to have substituted one multivalent cation for another and one active agent for another as taught by Jensen et al. with reasonable expectation of success. Appellants respectfully disagree.

The Examiner has once again misrepresented the teachings of a reference used in a rejection. First, the claims of U.S. Patent '835 do not recite just any multivalent metal cation, but instead recites the *salt* of a multivalent cation. Thus the multivalent metal ion is complexed with the salt and not the therapeutic agent. The present claims require that the multivalent cation be complexed with the active agent. The Examiner has provided no rational basis as to why the skilled person would be motivated to complex any compound with the active agent generally or a multivalent metal cation in particular.

In addition, the Examiner does not provide any basis or motivation with regard to the substitution of albuterol as claimed in U.S. Patent '835 with a therapeutic agent that form a complex with a metal cation, such as a protein and particularly insulin. The claims of U.S. Patent '835 generally recite a therapeutic, prophylactic or diagnostic agent and specifically recite only albuterol as a therapeutic agent. There is no general disclosure of even a protein as a suitable therapeutic agent and no specific disclosure of

insulin. Given the myriad of potential therapeutic, prophylactic or diagnostic agents known in the art, the choice of insulin, for example, was clearly not obvious.

In view of the above discussion, the Examiner has failed to established obviousness-type double patenting between the referenced claims in combination with the cited art and the present claims. Withdrawal of the rejection is respectfully requested.

Basu in view of Jensen

Claims 1-8, 10, 13-17, 24-28, and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of Basu (U.S. Patent No. 7,048,908) in view of Jensen et al. (6,043,214). OA mailed April 24, 2009. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The Examiner asserts that the claims of U.S. Patent '908 are drawn to a method of delivery to the pulmonary system comprising administering to the respiratory tract of a patient a bioactive agent in association with a charged lipid wherein the charged lipid has an overall net positive charge and the agent has an overall net negative charge. The Examiner asserts that the difference between the referenced claims and the pending claims is that, in the U.S. Patent '908, the multivalent metal cation is not identified. In the instant application, the multivalent cation of choice is zinc. The Examiner alleges that Jensen et al. teaches that zinc insulin complexes are known and beneficial for sustained release therapy and concludes that one of ordinary skill in the art would have been motivated to have looked in the art for specific multivalent metal cations suitable for combination with insulin, as taught by Jensen et al. with reasonable expectation of success. Applicants respectfully disagree.

The Examiner is misleading when she states that: "Jensen et al. teaches that zinc insulin complexes are known and beneficial for sustained release therapy". Jensen never discloses or suggests that the purpose for the complexation of a multivalent metal cation (e.g. zinc) with a therapeutic, prophylactic or diagnostic agent is for sustained release therapy, but rather states that it is for the purpose of improving stability and flowability. See FF8 of the Decision on Appeal dated February 24, 2009.

The Examiner is further misleading when she states that "in U.S. Patent '908, the multivalent cation is not identified". Nowhere in the claims of U.S. Patent '908, is there specific language claiming use of a *multivalent metal cation*. The referenced patent discloses a charged lipid associated with the bioactive agent. The Examiner provides no rational basis as to why the skilled person would substitute a charged lipid for a molecule of a completely different class such as a multivalent metal cation generally or zinc specifically. Also the present claims require that the multivalent metal cation be present in the amount of 10% w/w of the total weight of the agent. Neither the U.S. Patent '908 nor Jensen disclose or suggest this feature of the present claims. The referenced claims of U.S. Patent '908 are silent with regard to this feature, and as discussed earlier, calculation of the amount of zinc disclosed by Jensen as compared to the total weight of the agent is less than 1 %.

The present claims also require that the powder be spray dried. Neither the claims of U.S. Patent '908 patent nor Jensen disclose that the powder is spray dried. As stated by the Appeal Board in the Decision on Appeal dated February 24, 2009, the requirement of spray drying in the present claims can not be ignored. Page 11, Decision on Appeal dated February 24, 2009.

As discussed earlier, Jensen teaches away from the stabilized preparations disclosed in U.S. Patent '908. Jensen's dry powders are produced by a precipitation process that results in dry powders that are mostly crystalline particles. Jensen specifically states that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. In contrast, U.S. Patent '908 claims particles for drug delivery to the pulmonary system consisting of specific tap densities, aerodynamic size and median geometric diameters (see claims 15-20, Col. 31, lines 54-66). The crystalline particles resulting from the precipitation process disclosed by Jensen are fundamentally different from those disclosed in U.S. Patent '908. A precipitation process such as that disclosed in Jensen does not, by its nature, provide one skilled in the art with the means to control the formation of the crystals from the precipitate such that the resulting crystals are hollow and/or porous and possess desired tap density, aerodynamic and geometric sizes of the stabilized formulations of U.S. Patent '908. Therefore, one skilled in the art

would not be motivated to combine Jensen and U.S. Patent '908, as Jensen teaches away from a process and a product such as that described in U.S. Patent '908.

In view of the above discussion, the Examiner has failed to establish obviousness-type double patenting between the referenced claims in combination with the cited art and the present claims. Withdrawal of the rejection is respectfully requested.

Lipp '182

Claims 1-2, 4, 8, 10, 13-17, 24-28, and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 7,279,182 ("Lipp"). OA mailed April 24, 2009 The Examiner states that, although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The Examiner alleges that the referenced claims of U.S. Patent '182 are drawn to a method of preparing particles having the claimed tap density, geometric and aerodynamic diameters comprising forming a mixture including a therapeutically active agent, a hydroxydicarboxylic acid, a phospholipid, a solvent and a multivalent cation or anion and wherein the particles are spray dried. The Examiner further asserts that the claims of the instant application are drawn to a method of delivery to the pulmonary system of the particles made as in '182. Applicants respectfully disagree.

As discussed earlier with regard to related U.S. Patent '835, U.S. Patent '182 does not claim just any multivalent metal cation, but instead recites the *salt* of a multivalent cation. Thus the multivalent metal ion is complexed with the salt and not the therapeutic agent. The present claims require that the multivalent cation be complexed with the active agent. The Examiner has provided no rational basis as to why the skilled person would be motivated to complex any compound with the active agent generally or a multivalent metal cation in particular.

In view of the above discussion, the Examiner has failed to establish obviousness-type double patenting between the referenced claims and the present claims. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. Given the extensive rejections presented by the Examiner and the need for a lengthy response, the above arguments do not attempt to present the additional limitations of each of the dependent claims that have been rejected. The failure to do so in this reply should not be viewed as an admission that the claims in each rejection stand or fall together.

If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under § 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

Respectfully submitted,

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